GLUCOSE METABOLISM IN THE CRITICALLY ILL

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by

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ABSTRACT

Hyperglycaemia occurs frequently in the critically ill, even in those without a history of diabetes, and is associated with adverse outcomes. While the gastrointestinal tract is pivotal in the regulation of glucose metabolism in health and diabetes, this relationship had not been explored in the critically ill. The focus of this thesis is glucose metabolism in the critically ill, with a particular emphasis on the role of the gastrointestinal tract in modulating blood glucose concentrations. The work submitted for this thesis comprises two studies validating methodologies and eight subsequent studies.

In health, hormones secreted from the small intestine have the capacity to modulate gastric emptying. Studies were designed to further evaluate hormonal mechanisms underlying gastric emptying. The student established that in health endogenous glucagon-like peptide-1 (GLP-1) slows gastric emptying and glucose absorption, thereby attenuating postprandial glycaemia (chapter 4.2).

In the critically ill, glucose absorption was quantified following small intestinal administration, and it was observed that absorption was markedly impaired when compared to health (chapter 5.2). Despite the reduction in glucose absorption, postprandial glycaemic excursions were sustained for longer in the critically ill, attesting to the marked disturbance in glucose disposal in this group.

The current management of ‘feed-intolerance’ in the critically ill involves delivery of nutrient via a postpyloric catheter, or administration of a gastrokinetic drug during intragastric feeding. When comparing postpyloric and intragastric delivery of nutrient the student observed that the former route is associated with more rapid glucose absorption and exaggerated ‘early’ glycaemic excursions, but no clear increase in overall absorption (chapter 5.3). In clinical practice postpyloric delivery of nutrient is recommended because this technique can increase delivery of nutrient, which is assumed to equate to an improvement in nutritional outcomes. However, the observations from the student’s previous study challenge this premise. A further study showed that a single dose of erythromycin acutely increased small intestinal glucose
absorption, but possibly reduced lipid absorption and slowed small intestinal transit 
(*chapter* 5.4).

A series of studies examined the potential for a novel method to glucose-lowering in 
the critically ill by administering GLP-1 in pharmacological doses. It was shown that 
GLP-1 markedly attenuated the glycaemic response to small intestinal feeding in non-
diabetic critically ill patients (*chapter* 6.2), but that this effect appeared to be more 
modest in those patients with pre-existing diabetes (*chapter* 6.3). The mechanisms 
underlying the glucose-lowering effects of exogenous GLP-1 in the former group were then studied in more detail (*chapter* 6.4). In the critically ill pharmacological 
doses of GLP-1 have insulinotropic and glucagonostatic properties. Furthermore, 
exogenous GLP-1 has the capacity to reduce the rate of carbohydrate absorption as a 
result of slowing gastric emptying when the latter ‘normal’, but not when it is 
delayed.

In summary, the studies described in this thesis have yielded a number of novel and 
important insights. These include the mechanisms underlying glucose absorption in 
health, quantification of glucose absorption in the critically ill, and the use of a 
potentially novel therapy (GLP-1) to regulate glycaemia in the critically ill.
DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Adam Matthew Deane
27 February 2012
PUBLICATIONS

A proportion of the work presented in this thesis has also been published in peer-reviewed journals. The section of the thesis where this published work is included is provided below:


A proportion of the work presented in this thesis has been submitted for publication in peer-reviewed journals. The section of the thesis where such work is included is provided below:

ACKNOWLEDGEMENTS

The studies described in this thesis were collaborative projects in which I was one of many contributors. The work of other researchers was pivotal to the success of these studies.

It was with much good fortune that three exceptional supervisors and mentors were available throughout this PhD. Professors Robert Fraser, Marianne Chapman and Michael Horowitz provided incisive intellectual input, leadership, gentle guidance, humour, and friendship throughout this programme. While no records for the fastest time ever to complete a thesis were broken during my studies, it is quite possible that a new benchmark for coffees consumed with supervisors during a PhD programme (which encouraged much intellectual debate), and that is something that I enjoyed immensely and will always cherish.

The involvement of research scientists was absolutely essential to the completion of these studies. When I commenced the PhD I was fortunate to have Carly Burgstad and Laura Besanko, both experienced and knowledgeable research scientists, to provide technical expertise. Later in the programme Antony Zaknic and Matthew Summers became collaborators. Their enthusiasm, good humour, diligence, and friendship were invaluable. It was also very rewarding for me to see their intellectual progress and personal development throughout the programme.

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The involvement of the Royal Adelaide Hospital Intensive Care Unit Research Nurses, coordinated by Mrs. Stephanie O’Connor, was essential throughout my candidature. In addition, the support received from all of the Royal Adelaide Hospital Intensive Care Unit Nursing and Medical staff was also invaluable to the completion of these studies, and their assistance was greatly appreciated. I was very fortunate to have the involvement of experienced, enthusiastic, and good-humoured collaborators.
in addition to my supervisors, such as Associate Professor Chris Rayner and Professor Karen Jones. The intellectual and technical assistance of Ms. Julie Stephens, Mr. Max Bellon, and Mrs. Anne Maddox was essential to the performance of scintigraphic studies. Ms. Judith Wishart performed the analyses for insulin, glucagon and glucagon-like peptide-1 concentrations, and these were also essential to the studies performed. Statistical guidance was provided Ms. Kylie Lange. Kylie’s acceptance of the inherent difficulties of undertaking studies in the critically ill was particularly valued. It is also important to acknowledge the time and efforts of the Royal Adelaide Hospital Human Research Ethics Committee (RAH REC). The RAH REC has taken the time to understand the unique clinical scenarios that occur in the critically ill patients we wish to study, as well as having intimate knowledge of the expertise that the group of collaborators working on these studies have. Without a local Research Ethics Committee the studies described in this thesis, which require sophisticated methodologies, may well have been unnecessarily delayed or modified. The assistance of Sharon Yap, Ms Ying Shi Chan, and Ms Sally Michail from the Department of Pharmacy, Royal Adelaide Hospital, was also vital. The Department of Pharmacy were responsible for randomisation and prepared study drugs such that allocation concealment was maintained in all of the studies.

I was also fortunate to receive financial assistance throughout this programme that ensured that the studies could be undertaken. These included a co-funded University of Adelaide/Royal Adelaide Hospital Dawes Scholarship that afforded periods of full-time study. Project grant funding from the National Health and Medical Research Council (NH&MRC) of Australia, Royal Adelaide Hospital Special Purposes Fund, and the Australian New Zealand College of Anaesthetists were also essential.

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ABBREVIATIONS USED IN THE THESIS

3-OMG 3-O-Methyl-Glucose
ADA American Diabetes Association
ARDS Acute respiratory distress syndrome
APD antropylorduodenal
APACHE Acute physiology and chronic health evaluation
AWs Antral waves
CCK Cholecystokinin
DPP-4 dipeptidyl peptidase-4
EDTA Ethylenediaminetetraacetic acid
ELISA Enzyme-linked immunosorbent assay
ex(9-39)NH₂ Exendin(9-39)amide
GEC Gastric emptying coefficient
GH Growth hormone
GIP Glucose-dependent insulinotropic polypeptide
GLP-1 Glucagon-like peptide-1
GRV Gastric residual volume
GTN Glycel trinitrate
HbA₁C Glycated haemoglobin
HPLC High-performance liquid chromatograph
ICU Intensive care unit
IPPWs Isolated pyloric pressure waves
L-NAME L-Nitro-arginine methyl ester
L-NMMA L-Nitro-monomethyl-arginine
MMC Migrating motor complex
MRI Magnetic resonance imaging
NANC Non-adrenergic non-cholinergic
NEFA Non-esterified fatty acids
NH&MRC National health and medical research council
NO Nitric oxide
POC Point-of-care
PN Parenteral nutrition
PYY Peptide YY
SGLT-1 Sodium glucose cotransporter-1